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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/473,830	12/28/1999	JEFFREY M. LEIDEN	2844/53802	1518

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 10/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/473,830	LEIDEN ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 10 September 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.☒ A Notice of Appeal was filed on *21 September 2004*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2.☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see Note below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____.

3.☐ Applicant's reply has overcome the following rejection(s): _____.

4.☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6.☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: *None*.

Claim(s) objected to: *None*.

Claim(s) rejected: *24-30,32,33 and 35-47*.

Claim(s) withdrawn from consideration: *None*.

8.☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9.☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10.☐ Other: _____

Shin-Lin Chen
Primary Examiner
Art Unit: 1632

Continuation of 5. does NOT place the application in condition for allowance because: Applicants amended claim 41 to read on antisens RNA or a protein capable of inducing angiogenesis or is capable of inhibiting angiogenesis and cite Dr. Phamacek's declaration. Applicants argue that since markers and angiogenic proteins can be introduced by the claimed method, other molecules capable of inducing or inhibiting angiogenesis could also be introduced to achieve stable and efficient transduction by the same method (amendmen p. 6). Applicants further argue that intraventricular or intracardiac injection of rAAV vector encoding an antisense RNA for angiotensinogen receptor (AT1-R) reduces blood pressure and slows development of hypertension in rats, and alkaline phosphatase reporter gene was expressed in the carotid adventitia of cynomolus monkeys using rAAV vector (amendment, p. 7). This is not found persuasive because of the reasons of record. The unpredictability of the art of gene therapy in vivo is as discussed in the preceding official actions mailed 9-10-03 and 4-22-04. Gene therapy protocols using nucleotide sequences encoding different proteins differ from each other because different proteins have different biological functions and their stabilities inside cells and corresponding disease to be treated could vary. Different diseases differ from each other pathologically and they require nucleic acids encoding different proteins for treatment. The claims still encompass using antisense RNA or protein capable of inducing angiogenesis or inhibiting angiogenesis. The mechanisms of antisense RNA and nucleic acid encoding a therapeutic protein for treating a heart disease differ from each other and require separate consideration in the context of gene therapy in vivo. Therefore, gene therapy using nucleotide sequences encoding different proteins or antisense RNA for various diseases are considered case by case. Although Dr. Phamacek indicates that intraventricular injection of AAV encoding AT1-R antisense RNA reduced blood pressure and slowed the development of hypertension in rats, it does not mean that any antisense RNA, for example antisense RNA capable of inducing angiogenesis or capable of inhibiting angiogenesis, would be able to provide therapeutic effect in vivo foir a particular disease. Each antisense RNA has to be considered individually for its effectiveness in providing therapeutic effect in vivo because they differ in their nucleotide sequence, sequence specifici to the target sequence and their stability in vivo. The specification states "Protein useful for treating restenosis include thymidine kinase, cytosine deaminase, p21, p27, p53, Rb, and NF-kapaB (e.g. p. 5). The mechanism of treating restenosis differ dramatically from that of inducing angiogenesis in vivo. A successful gene therapy protocol can not be extrapolated into a successful result for another gene therapy protocol. Therefore, intracoronary injection of rAAV vector expressing an angiogenic protein, such as FGF protein and VEGF protein, may be able to provide therapeutic effect in vivo, but it is not necessary that thymidine kinase, p21, p27, p53, Rb or NF-kapaB would be able to provide therapeutic effect in treating restenosis in vivo via the claimed method. The state of the art in gene therapy in vivo and the teaching of the present invention fail to provide sufficient enabling disclosure to enable the full scope of the invention claimed Thus, claims 41, 42, 44, 46 and 47 remain rejected under 35 U.S.C. 112 first paragraph. Applicants argue that Hammond does not teach specific dosage of AAV to be administered and does not teach stable and efficient transduction. Applicants also argue that the cited claims do not recite FGF or VEGF and Hammond teaches injection of adenovirus not AAV (amendment, p. 9-10). This is not found persuasive because of the reasons of record and Hammond teaches a method for treating patient with congestive heart failure by delivering an AAV vector expressing FGF or VEGF to said patient via direct intracoronary injection of said AAV vector into coronary artery in an amount of AAV virus of 106-1014 particles or 108-1012 particles (e.g. p. 68-71). Claims 1 and 8-17 teach using a vector comprising a gene encoding an angiogenic protein, such as FGF-1, 2, 4, or 5, or VEGF. Claim 25 speficies the vector is a viral vector and claim 26 specifies the vector is a viral particle. Claim 28 specifies the viral particle is a rAAVand claim 29 specifies 106-1014 virus particles can be delivered. Therefore, Hammond teaches using a vector, including a rAAV, expressing an angiogenic protein, such as FGF-1, 2, 4, or 5. Although claim 29 does not depend on claim 28 which recites rAAV, however, claim 29 depends on claim 26 which recites any viral particle, including rAAV viral particle. The range of viral particles taught by Hammond in claim 29 applies to any viral particle, including rAAV particles. When a patient's average body weight is 60 kg, i.e. 60000gm, the amount of AAV virus injected to each patient would be 17 to 1.7x109 particles/gm body weight. The range of the AAV virus administered in the present invention falls within the range of the AA virus taught by Hammond. Thus, the dosage of AAV viral particles taught by Hammond anticipates the dosage of the claimed invention. Further, the specification fails to specifically define the phrase "stable and efficient transduction". Stable and efficient transduction does not mean that the nucleotide sequence has to be integrated into the genome of the cells. Transient expression of the encoded gene in th cell is considered "stable and efficient transduction".Applicants argue that neither claim 29 or 30 recite AAV or depend from a claim that recites AAV and neither claim 26 or 27 recite AAV. Applicants further argue that claims 26 and 28-30 fail to teach delivering the recited dosage of rAAV vector expressing FGF or VEGF to a patient (amendment, p. 10-11). This is not found persuasive because of the reason set forth above and that Hammond teaches "Presently preferred are viral vectors, particularly replication-defective viral vectors (including ...adeno-associated virus (AAV) vectors". AAV vector is preferred viral vector. Thus, claims 24, 32, 33, 40, 43 and 45 remain rejected un der 35 U.S.C. 102(a). Applicants argue that Hammond does not teach using 108-1012 rAAV particles, instead it is adenovirus particles (e.g. amendment, p. 12). Examiner conceds that it was an error by examiner, however, examiner does states that Hammond teaches using 106-1014 AAV viral particles in the Official action mailed 9-10-03.Applicants argue that Hammond does not teach stable and efficient transformation of cardiomyocytes or suggest administering an amount of any virus necessary to achieve stable transduction of cardiomyocytes (e.g. p. 12-13). This is not found persuasive because of the reasons of record and the reasons set forth above. Thus, claims 24-30 and 35-39 remain rejected under 35 U.S.C. 103(a) .